THE PROPOSED WORK FOR THE AWARD OF DEGREE OF

DOCTOR OF PHILOSOPHY IN CHEMICAL SCIENCES

A SYNOPSIS

Design, Synthesis and Biological Activities of Novel Heterocyclic Conjugates

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By

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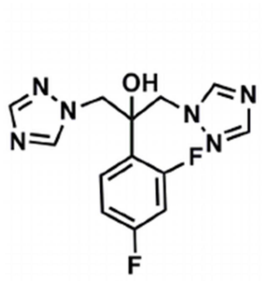
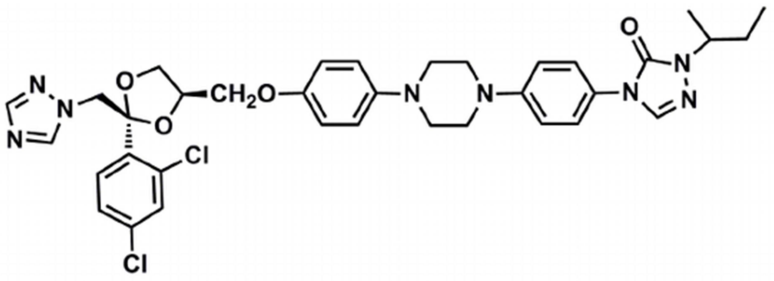
Introduction:

Medicinal chemistry which is becomes an important field in chemistry because the interface chemistry and the medical life issues by trying to study the common diseases and how should we solve it. Heterocyclic compounds have exhibited exciting medicinal applications including anticancer. Some market selling heterocyclic anticancer drugs include 5-flourouracil, methortrexate, doxorubicin, daunorubicin, etc.. Besides , some natural products including vinblastine and vincristine having basic frame work of heterocyclic moieties are used as anticancer drugs. Overall, heterocyclic moieties have always been core parts in development of novel and efficacious drug molecules. Some of the triazole based drug molecules shown below signify the importance of this class of compounds in medicinal chemistry. In addition, some market selling anticancer heterocyclic compounds have been highlighted.

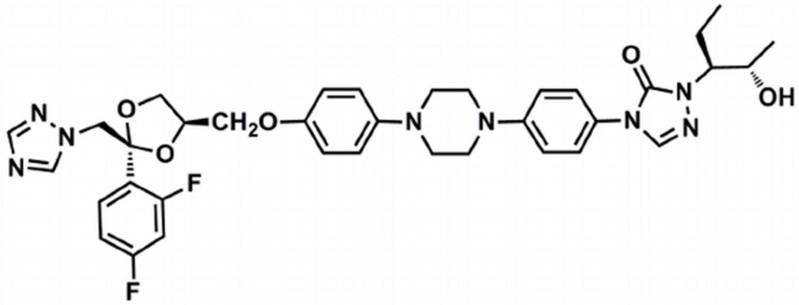


Fluconazole



Itraconazole

Voriconazole



Posaconazole

Since being first introduced by Dr. Barry Sharpless' group in 1999 at the 217th American Chemical Society annual meeting, click chemistry has become a very popular topic, as evidenced by a nearly exponential growth in the amount of related publications. A literature search via Sci Finder Scholar, revealed that a total of 788 publications containing the keywords "click chemistry" or "click reaction", which included journal articles, reviews, preprints, abstracts, patents, and dissertations.[1].

The term "click chemistry" was first introduced by Sharpless and co-workers in 2001. It describes a modular approach to organic synthesis, rapidly creating molecular diversity using only a small number of near-perfect reactions. Click reactions are defined by a stringent set of criteria: they must be efficient and selective, but at the same time wide in scope, giving consistently high yields with a variety of starting materials. The reactions must be easy to perform, be insensitive to oxygen or water, and use only readily available or accessible reagents. Furthermore, reaction work-up and product isolation must be simple, ideally without requiring chromatographic purification [2]

The chemistry involving triazoles has a significant role due to their medicinal and industrial properties as drugs and intermediates respectively in various areas.[3,4]The aspects of stability to metabolic degradation, association with drug targets,5the formation of hydrogen-bonds makes triazole as pharmacophore in many biologically active molecules. These are well-known compounds for diverse biological activities like anticancer, antimicrobial, antifungal, anti tubercular, anthelmintic, analgesic, anti-inflammatory and anticonvulsant. Also, 1,2,4-triazoles are evident for possessing central nervous system (CNS) acting drug candidates

(stimulants, anxiolytics) and effective on enzymes like cholinesterase inhibition[5], etc**.**

Origin of research problem:

"Click" chemistry word has introduced by Sharpless, Finn and Fokin in early 21st century and tell of methodology of neat modifying of substances by joining small units together. The "Click" chemistry has made an extensive contribution to many areas of modern chemistry from small molecule synthesis to drug discovery to materials science. Reactions united by the "click" family have a strong energy driving force that ensures starting compounds to react promptly, competently, and with no undesired byproducts even under physiological conditions, which make these transformations perfect models of biorthogonality. Examples of "click"-reactions include Copper-Catalyzed Azide-Alkyne Cycloaddition (CuAAC) Reaction, Strain-Promoted Azide-Alkyne Cycloaddition (SPAAC) Reaction, Strain-Promoted Alkyne-Nitrone Cycloaddition (SPANC) Reaction, Alkene and Tetrazine Inverse-Demand Diels-Alder Reaction, Alkene and Tetrazole Photoclick Reaction, Thiol–ene "click" reaction, Sulfur Fluorine Exchange (SuFEx) reaction etc. Moreover, the conjugtaqed hetterocyucles constitutes important medicinally previledged scaffolds[6].

Interdisciplinary Relevance:

Click chemistry involves highly efficient organic reactions of two or more highly functionalized chemical entities under eco-friendly conditions for the synthesis of different heterocycles. Nucleophilic ring-opening reactions, cyclo-additions, nucleophilic addition reactions, thiol-ene reactions, Diels Alder reactions, etc.these are several organic reactions included in click reactions. These organic reactions have main features i.e. high functional group tolerance, formation of a single

product, high atom economy, high yielding, no need for column purification, etc. It procure number of applications in drug discovery, supra molecular chemistry, material science, nanotechnology, etc.

In designing drugs, there is huge demand for eco-friendly pathways to accomplish the green aspects of chemistry. Novel green pathways play a essential role in the synthetic chemistry field by suppression of harmful solvents and chemicals or suitable handling of waste materials. The quest for new and proficient approaches for the synthesis of many biologically active scaffolds has made click chemistry a promising approach in chemistry. Click chemistry is a useful approach for the fabrication of molecules.

Click chemistry was introduced by K. Barry Sharpless in 2001. The term click chemistry not only mention to the reaction which occurs fast but also to those that involve twelve principles of green chemistry *i.e.* selective, easier product isolation, mild reaction condition, high yield, good atom economy, avoid toxic catalyst and solvent, and so on. They enclose reactions that are high yielding, fast, modular, and wide in scope. They are practical and unbiased for a variety of functional groups. Finally, the product isolation is expected to be effortless due to lack of by-products. These vast characteristics make click chemistry a powerful tool that covers a path in several fields of research *viz.* designing of drugs and lead structures[7].

The click chemistry has been such an interesting topic of research that many review articles have been published so far which explained its applicability in various fields of chemistry like manufacturing and alteration of metal–organic frameworks , making devices in bio-sensing system for responsive copper identification , designing bio-adhesives for hastening wound closure , in virus-

related research , generation of biosensors , proteomics analysis , in strategy for indirect ^{8}F-labeling[9] , *in vivo* bio-imaging[10] , to identify the interaction of curcumin with protein , synthesis of polymers and material science , for surface modification and so on.

Review of Research:

Aim and Objectives :

The proposed research is directed with the goal of understanding the Biological applications of Triazole based conjugates.1,2,3-triazoles are stable towards metabolic degradation and easily form *hydrogen* bonding which can increase solubility favoring the binding of bio molecular targets Owing to their unique properties, 1,2,3-triazoles are attractive building blocks in drug discovery.

The main biological applications of the 1,2,3-Triazoles are anti-inflammatory , anti-diabetics, antifungal and antibacterial activity. If time permits, all the compounds synthesized so far could be screened for some other important biological activities like anticancer and antioxidant activities etc.

Objectives:

1) To design structural Library of Triazole conjugates.
2) To synthesize various Triazole conjugates containing ether, ureiod and amide moieties..
3) To characterize the synthesized compounds by different analytical techniques such as ^{1}H NMR, ^{13}C NMR, HRMS etc,
4) To screen the synthesized compounds for their in vitro anti-inflammatory , anti-diabetics, antifungal and antibacterial activity. If time permits, all the

compounds synthesized so far could be screened for some other important biological activities like anticancer and antioxidant activities etc.

National and International Status:

Medicinal Chemistry is a discipline at the intersection of chemistry, especially synthetic organic chemistry, and pharmacology and various other biological specialties, which are involved with design, chemical synthesis and the development to market bio-active molecules, or pharmaceutical agents (drugs).

National Status:

There are large number of groups working nationally and internationally in titled area. At the national level , the group of **Prof.Bharatam** at NIPER Mohali is working in the design and synthesis of novel heterocyclic conjugates as antimalerial and anti-diabeatic agents. In addition , the group of **Prof. Guchhait** at same Institute is working on Design and synthesis of novel heterocyclic compounds as human DNA topoisomerase IIα inhibitors, Microtubule-dynamics inhibitors, DNA polymerases inhibitors, and their SAR studies as well as Design and synthesis of heterocyclic compounds as target-specific antileishmanial agents[8]. Regarding Click Chemistry, the group of Prof V. K. Tiwari at Banarus Hindu University (BHU) is exploring the concept of Click chemistry for synthesis of medicinally important dendrimers. For example, the group have developed the "Click" inspired Synthesis of hexa and octa decavalent peripheral Galactosylated Glycodendrimer and their possible therapeutic Applications.

International status:

The group of **Prof. TANG Weifang** at china Pharmaceutical University working on Design, synthesis and biological evaluation of pan-Raf/Ret multi-target

inhibitors as antitumor drug. Professor Tang is the co-inventor of FN-1501,an anticancer agent in clinical trials.

Besides the group of **Prof. ZHANG's** at same university working interests involve the design, synthesis, biological evaluation and mechanism study of new drugs. Their recent research focuses on two main fields: i) the rational design and discovery of small molecules for the treatment of cancer or anemia by targeting ROS pathway and oxygen-sensing VHL-PHD-HIF system; ii) synthesis, SAR and drugability optimization studies based on natural products, such as bata-lapachone, tanshinone IIA, andgambogic acid.

Several bioorganic and medicinal chemistry groups are active at the School of Chemistry of Tel Aviv University. These include the following research areas: Natural product based drug discovery (Prof. Yoel Kashman and Prof. Shmuel Carmeli); Targeted drug delivery (Prof. Doron Shabat and Dr. Micha Fridman); Anti-metabolic and antibiotic drug development (Dr. Micha Fridman); Chemical ecology of natural products (Prof. Shmuel Carmeli).

Dr. Michaela Serpi at Cardiff University working in biological chemistry his interest encompasses several areas of drug discovery as the antiviral and anticancer fields as well as rare diseases and antimicrobial resistance.

Methododologies to be adopted:

A} **Synthetic methods**

The synthesis of novel Triazoles would be carried out via copper catalysed azide-alkyne cycloaddition reaction. The above synthesized Triazole derivatives would then be further converted into novel Triazolyl ether, ureas and sulfonamides .

These transformation would employ the etherification, addition to isocyanates, thiodocyanates and substituted aryl or alkyl sulfonyl chlorides of previously synthesized Triazolyl derivatives.

B} **Characterisation of compounds**

All the synthesized compound would be throughly characterized by state of arts analytical technology such as NMR, HRMS, IR etc. so as to elucidate their correct structure.

B) Biological activity evaluation:

A large pool of ureido, amide and ether conjugated 1,2,3triazole would be screened to evaluate their diverse biological activities aimed at discovery of novel lead molecules. The biological activity to be evaluated mainly include

a) anti-inflammatory

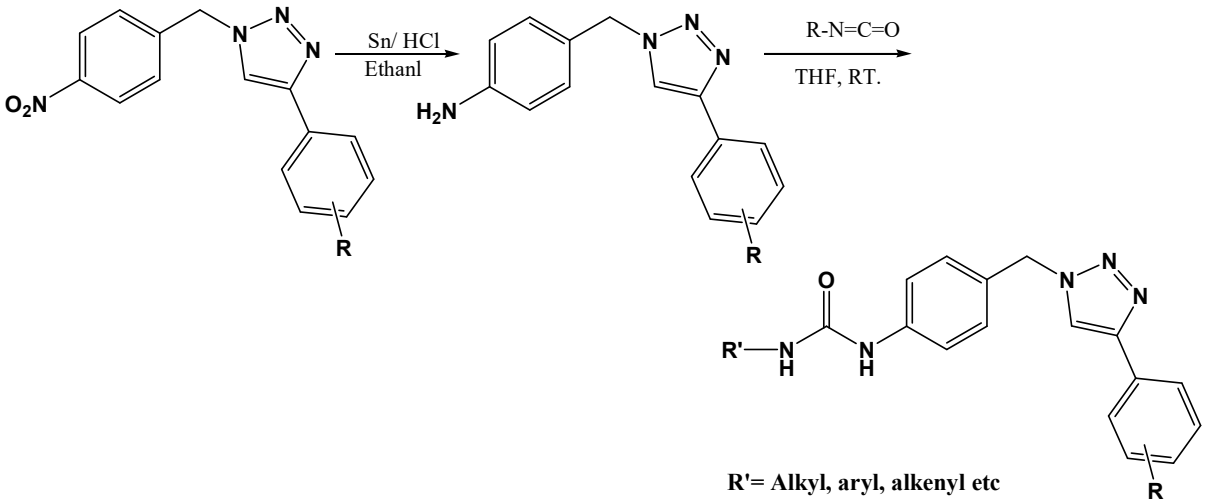
b) anti-diabetics

c) antifungal

d) antibacterial activity and

e)anti oxidant

D A representative Scheme for Synthesis:



Proposed yearwise work Plan :

1 st year :

In **1 st** year, the keen inspection of literature related to the theme of the proposed work would be carried out. The vast collection of literature would enable to design the novel and probable effective heterocyclic scaffolds for the various biological activities. Also, some important starting material such as complex azides and alkynes for the proposed work would be synthesized here.

2nd year:

The second year would be solely dedicated to synthesis of novel triazolyl amine and sulfonyl chlorides. These compounds constitute the key precursor for the synthesis of novel triazolyl ureas and amides that is novel heterocyclic conjugates as proposed in the title of the research work.

3rd year:

In this period, the synthesis and biological activity evaluation of novel heterocycles and ureides heterocyclic conjugates would carried out. The various ureido and amido conjugated heterocycles would be fully characterized by modern analytical methods such as NMR, HRMS, IR etc. The library of above compounds so synthesized would be then screened to evaluate their various biological activities such as anti-inflammatory, anti malerial and antibacterial activity. Finally compilation, interpretation of data obtained during the above period and thesis writing would be done in this year.

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